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Unusual association of diseases/symptoms

Severe consequences of carbamazepine exposure in utero

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Summary

The 'foetal carbamazepine syndrome' is characterised by facial dysmorphism associated to cardiovascular, nervous system, urinary tract and skeletal anomalies. The authors present the case of a neonate born to a 33-year-old epileptic woman treated with long term carbamazepine (CMZ) therapy. Four of her pregnancies exposed to the drug showed bad outcomes. The actual pregnancy ended by caesarean section, a female was born showing facial dysmorphism, hypoplasic nails, xyphosis and myelomeningocele. After 7 days of birth, the infant developed severe neutropenia, moderate pulmonary hypertension, multiple organ failure and died. The karyotype was 46, XX. This case represents an example of the wide spectrum of the syndrome and contributes to describe the clinical profile of the 'foetal carbamazepine syndrome'. The delineation of the foetal carbamazepine syndrome's phenotype remains incomplete, since many of the clinical manifestations are shared with the effect of others anticonvulsants, therefore further studies are needed to determine the specific noxious effects of CMZ in utero.

BACKGROUND

Carbamazepine (CMZ) is one of the first line antiepileptic drugs (AEDs) used in the treatment of other neurological and psychiatric diseases in pregnant women due to its low harmful potential. The prevalence of epilepsy in the general population is between 0.6% and 1%; and about 0.5% of all pregnant women have epilepsy. The treatment with anticonvulsant drugs (AEDs) increases the risk of malformations from 1.25 to 11%, which represents a four times greater risk than that observed in the offspring of healthy women. The overall effects of AEDs exposure in the foetus have lead to the description of the foetal anticonvulsant syndrome (FACS). The findings in foetus with FACS comprise a well known group of manifestations including mild to severe mental retardation, minor craniofacial dysmorphism associated to major malformations of the heart, kidney and neural tube defects. The clinical features of FACS differ slightly among the different AEDs used.

Several cohort studies have evaluated the risk of major congenital malformations associated with CMZ, and it seemed to be less teratogenic than other AEDs. Many reports described an increased rate of major congenital anomalies (MCA), especially of neural tube defects; while others suggest that CMZ probably does not substantially increase the risk of MCA. Some authors argue in favour of the existence of a 'foetal carbamazepine syndrome (FCS)'. Its main features will encompass prematurity, low birth weight and the presence of typical facial dysmorphism; including doll-like face with full cheeks, short nose, well defined philtrum and a relatively small chin; digital nail hypoplasia, reduced head circumference, a variable degree of development delay and neural tube defects. Previously reported CMZ-exposed cases show mild findings; and it has been difficult to establish which alterations can be feasibly attributed to the CMZ, because most of the patients with epilepsy take more than one medicine.[1 2]

We describe a newborn with several congenital malformations that died within the first week of life due to the severity of the abnormalities probably caused by in utero exposure to this drug.

CASE PRESENTATION

The mother was 33-year-old on her fourth pregnancy with previous history of epilepsy since age of 15, treated with oral CMZ 400 mg daily. Her first child has been diagnosed with absence seizures; the second and third pregnancies resulted in early spontaneous abortions. The mother refers mild tobacco use and occasional alcohol consumption during the entire pregnancy. The prenatal follow-up was poor, without control of CMZ serum levels'. She attended to a general practitioner's office at 8 weeks and at 24 weeks of pregnancy, no obstetric ultrasound was previously performed, she recorded to be seizure free. She attended to our hospital at 36.6 weeks with early signs of labour and symptoms of urinary infection. After an abnormal foetal tococardiography showing flat tracing with high variability, it was decided to perform a caesarean section. A female baby born, the birth weight was 1530 g, length 42 cm, occipitofrontal circumference 27 cm and the Apgar score was 5/9. The infant presented generalised hypotrophy, dolichocephaly and abnormal facies with narrow forehead, midfacial hypoplasia, a flat nasal bridge, prominent nasal tip, anteverted nostrils, large pinna, retromicrognathia, normal palate, xyphosis, lumbosacral myelomeningocele, hypotrophic lower extremities and hypoplastic nails (figure 1). Neurological exam shows hyporeactivity, absence of rooting and suction reflexes; deep tendon reflexes absence in lower extremities without spontaneous movement and absence of anal tone. Shortly after birth the neonate developed respiratory distress and required tracheal intubation, she was transferred to the intensive care unit to give ventilatory support. The echocardiogram

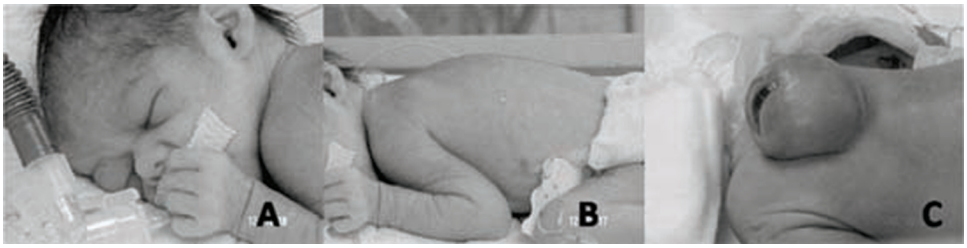

Figure 1 (A) The case with abnormal facies, narrow forehead, flat nasal bridge, prominent nasal tip, anteverted nostrils, midface hypoplasia, large pinna. (B) xyphosis. (C) lumbosacral myelomeningocele.

showed moderate to severe pulmonary hypertension without evidence of congenital cardiopathy. Antibiotic treatment was started because of infection suspicion. A complete blood count reported a hematocrit of 42%, 3840/mm^3 leucocytes, 19,000/mm^3 platelets and later developed severe neutropenia (480/mm^3 neutrophils). Blood cultures rule out a bacterial infection. At 7 days of life the baby developed severe respiratory alkalosis without response to treatment and died. The patient's karyotype revealed a normal 46,XX; expanded metabolic screening was also normal.

DISCUSSION

CMZ is a folic acid antagonist that increases the risk of neural tube defects and cardiovascular defects. The case reported here presents spina bifida added to the known craniofacial abnormalities that compose the FCS. Major malformations occasionally associated to CMZ exposure include cleft lip and cleft palate, skeletal and brain anomalies, absence of the gall bladder or thyroid, anal atresia, ambiguous genitalia, congenital dysplasia of the hip, inguinal hernia and torticollis; among others. Although there is not enough evidence if these major malformations are indeed associated to exposure to CMZ during pregnancy. Previous studies have postulated a higher risk of adverse pregnancy outcomes for women exposed to the drug explained by extreme teratogenic susceptibility to AEDs, as occured in two previous pregnancies in the mother of this case.[1 2]

Although the exact mechanism by which CMZ exerts its effects is still unknown, there are several theories; among them are the altered function of enzymes that metabolise or detoxify this compound, individual errors in folic acid metabolism or interference of gene expression by currently unknown mechanisms or individual variations in response to different amounts of drug exposure. Dean J *et al* investigate the methylenetetrahydrofolate reductase homozygous 677TT genotype as a risk factor for the FACS; they conclude this mutation caused three to four times higher risk to have affected infants. Until the whole individual risk factors are known, it is important to establish prevention strategies for pregnant women. The use of folic acid reduces the risk of neural tube defects, but not the presence of other malformations; and it is well known that the number of infants with malformations is less in those mothers taking folic acid antagonists who received supplements of this vitamin in the first 2 months of pregnancy.[3]

She also presented pulmonary hypertension and neutropenia which have not been previously reported in the FCS. The offspring of epileptic mothers treated with anticonvulsants is at a greater risk of developing haemorrhagic disease of the newborn and thrombocytopenia since this drug alters vitamin K metabolism. In serum from pregnant women exposed to AEDs, a precursor protein induced by the absence of vitamin K called protein induced in vitamin K absence (PIVKA) has been found. PIVKA could be quantified and used as a foetal haemorrhage risk marker. Therefore, vitamin K supplementation in pregnant women receiving anticonvulsant therapy is mandatory as a preventive measure. Besides the coagulation abnormalities, vitamin K could play a critical role in the nasal septum development and subsequent midfacial growth and these may contribute to the FCS phenotype.[4]

Our case developed neutropenia which has not been previously associated with the use of CMZ during pregnancy, however it occurs in patients when the drug reached toxic levels in haematopoietic organs. Idiosyncratic drug-induced agranulocitosis remains a serious adverse event associated in patients treated with CMZ caused either by the drug itself or a metabolite.[5]

In conclusion, the foetal effects of CMZ are quite variable, traditionally it has been considered as a safe drug in pregnancy however it may seriously affect craniofacial, neural tube, bone marrow and lung foetal development in susceptible individuals. Knowing the risks of CMZ prescription during pregnancy, epileptic women must be rigorously followed up for the early detection of foetal complications.

Learning points

- CMZ is one of the most commonly used antiepileptic drugs among pregnant woman. Prenatal exposure to CMZ causes a pattern of malformations that should be recognised early at birth. However it is one of the safest drugs to treat seizures in pregnancy.
- There are specific recommendations to woman taking anticonvulsants that should be followed after and during pregnancy. Including the use of higher-than-usual dose of folic acid, as this may help to protect the foetus.
- It should be taken in account that affected infants have minor anomalies associated to the drug use. Major malformations and lethality could occur as an individual susceptibility trait.
- Fatal consequences in exposed foetus could be expected, however improved prenatal care and neonatal interventions could help in less compromised cases.

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Competing interests None.

Patient consent Obtained.

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